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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/148,234	09/04/1998	IOANNIS MOUTSATSOS	P-4739-US	3002

49443 7590 05/26/2009

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
05/26/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/148,234	MOUTSATSOS ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/02/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/02/2009 has been entered.

Claims 1-23 have been cancelled. Claims 24 and 27 have been mended. Claim 29 is new.

Claims 24-29 are pending and under examination.

2. The objection to claims 24 and 27 for containing minor informalities is withdrawn in response to Applicant's amendments to the claims filed on 03/02/2009.

The rejection of claims 24-28 under 35 U.S.C. 112, first paragraph, as introducing new matter is withdrawn in response to Applicant's arguments filed on 03/02/2009. Specifically, Example 2 discloses transplantation of cells without mentioning a matrix. Moreover, the disclosure recites that, in some embodiments, the cells "may be administered in combination with an appropriate matrix" (p. 6, lines 28 and 29). Such a recitation indicates that the disclosure also encompasses the embodiment wherein cells are transplanted without a matrix.

Claim Rejections - 35 USC § 112, 1st paragraph - enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 24-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The instant claims are drawn to a method of inducing organized, functional bone formation at a site of bone infirmity by implanting genetically engineered MSCs in the absence of a supporting osteoinductive matrix (claims 24-28) or in the absence of any

support matrix (claim 29). However, neither the instant specification nor the art is enabling for the present claimed invention for the reasons discussed below.

Bone formation cannot occur by simply implanting MSCs in the absence of a support matrix (see Wolfe et al., Med. Prog. Technol., 1994, 20: 155-168, p. 159). The art clearly teaches that organized, functional bone formation requires retaining the cells and the factors secreted by the cells for a sufficient time to promote repair and bone growth, which can be accomplish only by using a support matrix. For example, Bruder et al. (J Cell Biochem, 1994, 56: 283-294, of record) teach:

> "In order to effect osseous repair in a local defect, the cells must be delivered to the site in an appropriate carrier. We envision the ideal vehicle as biocompatible to minimize inflammation, osteoconductive to foster integration, resorbable to promote its own replacement, supportive of mesenchymal stem cell attachment and porous to facilitate rapid vascularization. In many ways, this vehicle would functionally resemble hypertrophic cartilage of the growth plate or fracture callus".

Along the same lines, Leach et al. (Expert Opin Biol Theor, 2004, 4: 1015-1027, of record) teach:

> “Transplantation of bone-forming cells to a repair site can promote bone regeneration by direct participation of these cells in bone formation and by the release of osteoinductive factors by these cells.
>
> The infusion or injection of transplanted cells is limited due to their potential to migrate away from the repair site, apoptosis or necrosis. Physical association with carriers in various forms has proven to be an effective means for maintaining bioactive factors and cells at the desired location for prolonged time.”

Additionally, the instant specification fails to provide sufficient guidance for a skillet artisan on how to perform the claimed method. The specification provides only two examples of transplanting BMP-2-expressing cells without indicating whether a support matrix is used or not. Example 1 is directed to implantation into the abdominal muscle and not to a site of bone infirmity and therefore provides no guidance of how to

induce functional bone formation at a site of bone infirmity by implanting cells in the absence of a support matrix. Example 2 is related to transplantation of cells into a 3 mm bone gap. However, Example 2 only discloses that BMP-2-expressing cells are localized at the gap site one week after transplantation; there is no evidence that functional bone formation occurred. The remaining Examples all teach the use of collagen sponges comprising BMP-2 (i.e., osteoinductive matrices). Therefore, the specification does not teach how to induce organized, functional bone formation by implanting the cells without an osteoinductive matrix at a site of bone infirmity. The art does not teach such. In fact the art teaches that functional bone formation requires osteoinductive matrices to bridge gaps larger than 1 mm (see Vaccaro et al., Spine J., 2002, 2: 206-215, p. 207, column 1 and paragraph bridging columns 1 and 2). It is noted that even Applicant's own work (i.e., Moutsatsos et al., Molecular Therapy, 2001, 3: 449-461, of record) provides evidence that only co-implantation with an osteoinductive matrix leads to the induction of functional bone formation (p. 455, column 1; p. 458, columns 1 and 2; p. 459, column 2; p. 460, column 1). Interestingly, Moutsatsos et al. described the same experiment as the one disclosed in Example 2 and demonstrate that only the use of an exogenously added osteoinductive matrix leads to the healing of 3 mm gaps. Based on these teachings in the art and the lack of demonstration of functional bone formation in Example 2, one of skill in the art would not recognize that a gap of 3 mm could be healed by implanting BMP-2-expressing cells without a matrix. One of skill in the art would not recognize that implanting BMP-2-expressing MSCs in the absence of a support would lead to organized, functional bone

formation as claimed. In conclusion, it is considered that the invention, as presently claimed is not enabled.

Applicant argues, that cells expressing BMP-2 localize in a segmental defect, in the absence of any exogenously supplied matrix (p. 9, Example 2). Applicant argues that the transfected MSCs of the present invention were useful in building bone when administered with no matrix at all, only a collagen gel (Example 14). Further, Applicant argues, claim 24 has been amended and recites "implanting said cultured mesenchymal stem cell in the absence of an exogenously supplied osteoinductive matrix at a site of bone infirmity". Applicant submits that Examples 1-3, 8, 9, 11, 14 and 15 provide exemplification of transplantation *in vivo* of cultured BMP-2-expressing MSCs mounted in collagen sponges or gels. Applicant argues that Example 8 demonstrates that regulated expression of BMP-2 was highly effective in promoting bone formation at a segmental defect site, in the absence of an exogenously supplied osteoinductive matrix. Applicant maintains that the collagen sponge used in the above-mentioned Examples is not osteoinductive. Figure 6B of Moutsatsos et al. (Molecular Therapy 2003, 1: 449-461) shows that no bone was formed when a collagen sponge was implanted with C9 cells wherein the BMP-2 gene is shut off. Further, in Figure 4i of the same reference no bone formation is seen in an ectopic transplantation site. Applicants submit that Applicants have shown that MSC-BMP-2 appropriately home to the site of injury, align along defect edges, and are incorporated in newly formed bone trabecules, forming quantitatively and qualitatively superior bone. Thus, Applicant argues, the specification provides sufficient support in the form of exemplification to enable one skilled in the art

to make and use the claimed invention and accordingly, the rejection should be withdrawn.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

The examples were addressed in the rejection above. Applicant argues that the collagen sponge used in the above-mentioned Examples is not osteoinductive. This is incorrect. Any implant becomes osteoinductive when it contains osteoinductive factors (see Wolfe et al., Med. Prog. Technol., 1994, 20: 155-168, Abstract, p. 158, column 2, p. 159). The collagen matrix in the Examples comprises cells which are genetically engineered to express and secrete the osteoinductive protein BMP-2, which secreted BMP-2 is retain into the collagen matrix; therefore, the BMP-2-comprising collagen matrix is an osteoinductive matrix. The reference cited by Applicant (i.e., Moutsatsos et al., which represents Applicant's work disclosed in the instant specification) demonstrates that collagen matrices become osteoinductive when they comprise BMP-2 and provides evidence that only co-implantation with an osteoinductive matrix leads to the regeneration of functional bone; there is no teaching in the reference of implanting cell without a matrix. Therefore, Applicant has shown that only BMP-2-MSCs transplanted together with an osteoinductive matrix appropriately home to the site of injury, align along defect edges, and are incorporated in newly formed bone trabecules, forming functional bone. For these reasons, Applicant's arguments are not found persuasive, and the enablement rejection is maintained.

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633